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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ANANTH ANNAPRAGADA, RAVI V. BELLAMKONDA,
ERIC HOFFMAN, and CHANDRA VIJAYALAKSHMI

Appeal 2009-003511
Application 10/830,190
Technology Center 1600

Decided: September 10, 2009

Before TONI R. SCHEINER, LORA M. GREEN, and
FRANCISCO C. PRATS, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1-4, 6-11, and 25-33. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

Claims 1 and 25 are the independent claims on appeal, and read as follows:

1. A composition for enhancing contrast of one or more areas of a subject for X-ray imaging when administered to the subject, the composition comprising:

liposomes, each liposome encapsulating one or more nonradioactive contrast-enhancing agents, and each liposome comprising: cholesterol, at least one phospholipid, and at least one phospholipid which is derivatized with a polymer chain,

wherein the average diameter of the liposomes is less than 150 nanometers.

25. A composition for enhancing contrast of one or more areas of a subject for X-ray imaging when administered to the subject, the composition comprising liposomes, each liposome comprising:

at least one first lipid or phospholipid,

at least one second lipid or phospholipid which is derivatized with one or more polymers,

and

at least one sterically bulky excipient capable of stabilizing the liposomes;

wherein the average diameter of the liposomes is less than 150 nanometers, and wherein each liposome encapsulates at least one nonradioactive contrast enhancing agent.

The Examiner relies on the following evidence:

Payne	US 4,744,989	May 17, 1988

Vladimir P. Torchilin et al., "Poly(ethylene glycol) - coated anti-cardiac myosin immunoliposomes: factors influencing targeted accumulation in the infracted myocardium," 1279 BIOCHIMICA ET BIOPHYSICA ACTA 75-83 1996).

Andreas Sachse, PhD., et al., "Biodistribution and Computed tomography Blood-Pool Imaging Properties of Polyethylene Glycol-Coated Iopromide-Carrying Liposomes," 32 INVESTIGATIVE RADIOLOGY no. 1, 44-50 (1997)

Jens U. Leike, DVM, et al., "Characterization of Continuously Extruded Iopromide-Carrying Liposomes for Computed Tomography Blood-Pool Imaging," 36 INVESTIGATIVE RADIOLOGY NO. 6, 303-08 (2001).

We reverse.

ISSUE

The Examiner concludes that claims 1-4, 6-11, and 25-33 are rendered obvious by the combination of Tourchilin, Payne, and Sachse or Leike.

Appellants contend that the references relied upon by the Examiner, either alone or in combination, do not teach a liposome as required by independent claims 1 and 25 having an average diameter of less than 150 nanometers.

Thus, the issue on appeal is: Have Appellants demonstrated that the Examiner erred in concluding that the combination relied upon in the rejection teaches or suggests a liposome as set forth in independent claims 1 and 25 having an average diameter of less than 150 nanometers?

FINDINGS OF FACT

FF1 The Examiner rejects claims 1-4, 6-11, and 25-33[1] under 35 U.S.C. § 103(a) as being obvious over the combination of Torchilin, Payne, and Sachse or Leike.

FF2 The Examiner relies on Torchilin for teaching a liposome prepared by mixing the phospholipid phosphatidyl choline (PC), cholesterol, and a phospholipid derivatized with a polymer, polyethylene glycol dioleoylphosphatidylethanolamine (PEG-PE), wherein small liposomes having an average diameter of from 120 nm to 150 nm were formed (Ans. 4 (citing Torchilin, p. 77, first column, "*Preparation of Liposomes*")).

FF3 The Examiner finds that "prior to incorporation of the radioactively labeled contrast agent the targeted, pegylated liposomes of the disclosure include small liposomes of size 120-150 nm." (Ans. 4-5.)

FF4 The targeting agent was added to the liposomes of Torchilin by, when necessary, adding N-glutarylphosphatidtylethanolamine (NGPE)-antimyosin Fab to octyl glucoside (OG)-solubilized lipid mixture Torchilin, (p. 77, first column, "*Preparation of Liposomes*"). The NGPE-Fab is incorporated into the liposome membrane (*id.* at 70, first column, Results, *Immunoreactivity*).

FF5 The Examiner notes that Torchilin "does not disclose the encapsulation of an iodinated contrast agents [sic]." (Ans. 5.)

FF6 The Examiner relies on Payne for disclosing liposomes prepared from a combination of lipids and adjuvants, such as cholesterol, wherein the mean

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[1] The Examiner did not include claim 26 in the statement of the rejection, but notes that its exclusion was an inadvertent typographical error, and that the subject matter of the claim was dealt with in the body of the rejection (Ans. 2).

size of the liposome may be controlled to suit a particular medicament to be encapsulated in the liposome, such as an iodinated contrast agent (*id.*).

FF7 The Examiner also cites Payne for teaching that the mean size of the liposomes may be from about 100nm to 6 microns, and that the size of the liposome may be affected by the amount of phospholipids, pH, and hydration media (*id.*).

FF8 The Examiner also finds that Payne "does not teach or even suggest a liposome having lipids or phospholipids which are derivatized with a polymer." (*Id.* at 8.)

FF9 Thus, the Examiner relies on Payne for teaching "that liposomes of sizes 100 nm to 6 µm, which includes the less than 120 or less than 150 nm liposomes of the instant claims, may encapsulate a nonradioactive iodinated contrast agent." (*Id.*)

FF10 Payne teaches the formation of lipids containing a biologically active compound using a liposome-forming amphipathic lipid and, optionally, an adjuvant (Payne, col. 3, ll. 35-39), wherein the biologically active compound may be a contrast agent (*id.* at col. 6, ll. 11-41), and the adjuvant may be cholesterol (*id.* at col. 6, l. 54-col. 7, l. 8).

FF11 Payne teaches that "[i]t has been found that a predetermined degree of loading of the liposomal components on the carrier material . . . will facilitate ultimate formation of final liposome product of desired size, such as a mean diameter . . . of within the range of from 25 nm to about 12 µm and preferably from about 100 nm to about 6 µm." (*Id.* at col. 4, ll. 51-58.)

FF12 In the Examples, Payne prepares liposomes of, for example, 5.3 µm (col. 8, Example 1), 2.5 µm (col. 8, Example 2 and col. 9, Example 4), 5.3

µm (col. 9, Example 9). The smallest liposome actually prepared and measured by Payne is 0.16 µm (160nm) (col. 13-col. 15, Example 8, Table III).

FF13 The Examiner relies on Sachse for disclosing an iopromide-containing liposome for enhancing CT imaging, wherein the liposomes contain soy phosphatidylcholine (SPC), cholesterol, and soy phosphatidyl glycerol (SPG) (Ans. 5). The liposomes of Sachse are also derivatized with polyethyle glycol (PEG) using 5 mol% DPSE-PEG2000 (Ans. 5).

FF14 The Examiner relies on Sachse for teaching "liposomes containing soy phosphatidylcholine (SPC), cholesterol, soy phosphatidylglycerol (SPG) (6:3:1 molar ratio) and 5 mol% DPSE-PEG2000 which show prolonged blood circulation with CT density differences above 70 HU" (*id.* at 9), not for teaching "liposomes having polymer-chain derivatized phospholipids wherein the liposomes have an average diameter of less than 150 nm" (*id.*).

FF15 Sachse teaches that in the case of the DSPE-PEG derivatized liposomes, surface modification with PEG was accompanied "by a drastic increase in vesicle size," wherein the resulting mean diameter changed from 132 nm to 204 nm (Sachse, p. 3 of 8).

FF16 The Examiner relies on Leike for teaching a "computed tomography enhancing iodinated liposome composition containing soy phosphatidylcholine (SPC), cholesterol and soy phosphatidylglycerol (SPG)," wherein the liposomal agents have a mean diameter of 201 nm (Ans. 6).

FF17 The Examiner concludes that it would have been obvious to the ordinary artisan at the time of invention "to prepare targeted-pegylated

liposomes of the size 120nm-150nm (Torchilin et al.) and utilize/try them for the encapsulation of the iodinated contrast agents of Payne . . . as the liposomes of Payne . . . may also be 100 nm in size." (*Id.*)

FF18 According to the Examiner, the disclosures of Torchilin and Payne "are drawn to the same products (liposomes) and the encapsulation of the contrast agents of Payne . . . into the liposomes of Torchilin . . . will have predictable results, as there are multiple factors for controlling the size of the liposomes." (*Id.*)

PRINCIPLES OF LAW

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

While the analysis under 35 U.S.C. § 103 allows flexibility in determining whether a claimed invention would have been obvious, *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007), it still requires showing that "there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *Id.* "We must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention." *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008).

Moreover, an obvious to try rationale for supporting an obviousness rejection may also be improper in certain situations. The Court of Appeals for the Federal Circuit set forth *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988), two situations in which an "obvious to try" rationale was usually improperly applied. The first situation of "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters are critical or no direction as to which of many possible choices is likely to be successful." (*Id.*) The second situation of "what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *Id.* *See In re Kubin*, 561 F.3d 1351, 1358-60 (noting that the rationale in *O'Farrell* was "affirmed in the logical inverse" in *KSR*, 550 U.S. at 417, in the Statement that "§103 bars patentability unless 'the improvement is more than the predictable use of prior art elements according to their established functions.'").

ANALYSIS

Appellants argue that both independent claims, claims 1 and 25, require liposomes having an average diameter of less than 150 nanometers (App. Br. 9). Torchilin, Appellants assert, does not teach incorporation of an imaging contrast agent into the liposomes (*id.*). Appellants argue that Payne teaches that the composition of the liposomes influences their size, but does

not teach or suggest a liposome having a lipid or phospholipid that is derivatized with a polymer (*id.* at 10). Moreover, Appellants argue, the examples in Payne "almost exclusively demonstrate size of several microns." (*Id.*) Appellants argue further that the combination of references as set forth by the Examiner ignores the teaching of Sachse, who teaches that surface modification of liposomes with DSPE-PEG resulted in a dramatic increase in size, of from 132 nm to 204 nm (*id.* at 11). As to Leike, Appellants argue that Leike does not teach the use of phospholipids derivatized with a polymer chain, and the liposomes of Leike were about 200 nm in diameter (*id.* at 12).

Appellants argue further that the Examiner's assertion that it would have been obvious to try is improper as there was no reasonable expectation of success, as none of the references teaches how to make a liposome as claimed by independent claims 1 and 25.

We conclude that Appellants have the better position. Claim 1 requires a liposome comprising cholesterol, at least one phospholipid, and at least one phospholipid that is derivatized with a polymer chain, such as polyethylene glycol, wherein each liposome encapsulates one or more nonradioactive contrast-enhancing agents, and wherein the average diameter of the liposomes is less than 150 nanometers. Claim 25 is essentially drawn to the same liposome composition, but instead requires a lipid or phospholipid, at least one second lipid or phospholipid which is derivatized with one or more polymers, and at least one sterically bulky excipient capable of stabilizing the liposomes.

We agree with the Examiner that Torchilin teaches all of the elements of the composition, including the average diameter of the liposomes being less than 150 nm, except for the nonradioactive contrast-enhancing agent. However, the other references establish that the size of the liposome will vary once you start changing its composition.

Thus, Payne teaches formation of liposomes containing a biologically active compound using a liposome-forming amphipathic lipid and, optionally, an adjuvant, wherein the biologically active compound may be a contrast agent, and the adjuvant may be cholesterol. While Payne teaches that small sizes of less than 150 nm may theoretically be obtained, the smallest size actually obtained by Payne was 0.16 microns, and that liposome did not contain a non-radioactive imaging agent, nor did it include a lipid or phospholipid that is derivatized with a polymer chain.

Sachse, in our opinion, is in fact the most relevant of the references. That reference, as set forth by the Examiner, teaches all of the limitations of claims 1 and 25, except for the size. While the liposomes not derivatized with a polymer chain had a mean diameter of about 132 nm, when the liposomes were derivatized with DSPE-PEG, their size dramatically increased to 204 nm. Finally, in Leike, the liposomes did not include a polymer derivatized lipid or phospholipid, but did include a non-radioactive contrast agent, and had a mean particle size of 201 nm. Thus, we agree with Appellants that the references relied upon, either alone, or in combination, do not teach how to obtain a liposome composition as required by claim 1 and 25, wherein the average diameter of the liposomes is less than 150 nm.

We thus conclude that this is analogous to the first situation in *O'Farrell*, where application of an obvious-to-try rationale is improper. The situation is one where the ordinary artisan would need to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters are critical or no direction as to which of many possible choices is likely to be successful. The prior art demonstrates that the size of the liposomes is dependent on their composition. And while Payne in particular may give some general guidance, as seen from Sachse, even adding one additional component, in that case, derivatizing with a polymer, can, in the words of the reference, result in "a drastic increase in vesicle size." In particular, it appears as if the Examiner has found all of the pieces in the art, but provides no reason or rationale of how to combine them in manner that would lead to the claimed liposome composition.

CONCLUSION OF LAW

We conclude that Appellants have demonstrated that the Examiner erred in concluding that the combination relied upon in the rejection teaches or suggests a liposome as set forth in independent claims 1 and 25 having an average diameter of less than 150 nanometers.

We are therefore compelled to reverse the rejection of claims 1-4, 6-11, and 25-33 under 35 U.S.C. § 103(a) as being obvious over the combination of Torchilin, Payne, and Sachse or Leike.

REVERSED

Ssc:

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